REMARKS

Claims 5-11 are active and are drawn to the elected subject matter.

Claim 5 is amended to clarify that the APP is reduced in the brain as reflected in the specification on page 8, where plaque formation in the brain is reduced or prevented.

Applicants thank the Examiner for withdrawing the earlier applied rejections. In view of the following discussion, reconsideration and withdrawal of the new rejections applied under 35 USC 103(a) citing to DeMattos and Kojima and further in view of Boos is requested.

The Examiner finds that DeMattos suggests using antibodies against Aβ to remove Aβ from the brain and the blood. The Examiner acknowledges that DeMattos does not explicitly teach contacting the blood or plasma flow of a patient with an apheresis device that has the anti-Aβ antibodies attached to the surface of a solid carrier. It is further acknowledged that DeMattos administer the antibody directly to the animals with or at risk of disease.

Thus, reliance is placed on Kojima who teaches specific antibodies of β2MG or serum amyloid P are targeted using apherisis.

The Examiner finds that because DeMattos teaches that contacting blood with antibodies against the Aβ and is therapeutic for AD and sequestering of circulating Aβ in the periphery as taught by DeMattos one "would immediately understand that the methods of Kojima would also effectively remove circulating Aβ from the patients, if only they were modified to use an anti-A antibody rather than an antip2MG or anti-SAP antibody" (p. 4, 2nd paragraph of the Office Action).

A reasonable expectation of success alleged as Kojima demonstrates that the apheresis device is effective to remove circulating amyloid proteins. The Examiner further alleges that DeMattos shows that the method works *in vitro* across dialysis membrane as well.

These arguments, however, are erroneous and not based on the objective evidence in the references. Rather they are misinterpretations of the citations that are misapplied to reconstruct the claimed invention in hindsight. Conclusions of obviousness based on clearly erroneous findings, as is here the case, cannot stand. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

Kojima teaches the removal of an increased level of β2-MG from human plasma. The patients which undergo Hemodialysis (HD) in Kojima et al. have a 23- to 61-fold increase in β2-MG in their plasma over values for healthy individuals (see Kojima, p. 244, 4th paragraph).

In US 4,770,774, of record in this case, it is reported that such patients who are undergoing artificial blood dialysis for a long period have as high as 10 to 100 times higher β2-MG levels than normal human plasma levels (see US 4,770,774 A, col. 1, lines 29-35). Kojima therefore shows that an increased plasma level of p2-MG can be reduced in hemodialysis patients (see table 1 of Kojima). However, this reduced level in HD patients is still significantly higher than normal levels (see also table 1 of Kojima). IgE or SAP levels in plasma are shown to be decreased by applying the method. However, Kojima does not contain any information that amyloid depositions in certain compartments or even in the brain decrease with this method. Even if Kojima had shown reduction of several amyloid depositions, this would still only be a reduction within the blood system, i.e., in the periphery.

The present invention fundamentally differs from Kojima's approach, because apheresis is applied to the blood or plasma flow to reduce amyloid deposition, including APP, in the brain (and not in plasma). Plasma of AD patients does not have an elevated Aβ level. Quite in contrast, DeMattos shows a rapid 1000-fold increase in plasma Aβ. A corresponding β2-MG antibody has not been tested in Kojima. Therefore, it would be expected that such rapid increase in β2-MG does not occur, because the biology of the proteins in Kojima differs

so fundamentally from Aβ used in the context of the claimed invention. Accordingly, and in contrast to the Examiner's findings of obviousness, there can be no way to "immediately understand that the methods of Kojima would also effectively remove circulating Aβ from the patients" and apply this in shifting the equilibrium between blood and brain with respect to Aβ.

The Examiner argues that DeMattos shows that the method works *in vitro* across a dialysis membrane as well giving more weight to the contention of obviousness, presumably relying on p. 8851, left column, 3rd paragraph and Fig. 1A of DeMattos. The Examiner uses this passage to argue that "even in the absence of an immune system, the binding of Aβ to an antibody is sufficient to change the equilibrium of this small protein and allow for passage across a semi-permeable membrane".

This argument is erroneous and not at all supported by the underlying citations as would be understood by a skilled person. The *in vitro* system in DeMattos investigates the ability of an Aβ binding antibody to act as an Aβ sink for human cerebrospinal fluid (CSA). This experiment is conducted in an *in vitro* model for the influence of the equilibrium of Aβ between CSF and another compartment which — in this model — can only be blood. Taking the Examiner's construction of the prior art to its rationale conclusion to perform apheresis with the CSF of a patient, it is evident that the present method is not the same as nor would have been obvious for these simple facts known to that skilled person:

First, one would NOT conduct apheresis with CSF. This is why the claimed invention uses blood or plasma flow. On the other hand, the *in vitro* test and the results disclosed by DeMattos are contradictory: Whereas Fig. 1A and B simply show that m266 binds more specifically to Aβ than E4 or unspecific proteins (the "sequestration") is not a sequestration as later referred to in blood, but is simply a binding assay over a dialysis membrane.

Second, an appropriate *in vitro* test for the present invention would have had to provide a further membrane or compartment in the model of Fig. 1 A, wherein the antibodies are immobilized ("Bottom-Bottom Chamber") and providing in the Bottom Chamber Aβ itself instead of the Aβ antibodies and provide Aβ amyloid deposits above the dialysis membrane (the "Human CSF" compartment in Fig. 1A). However, this is neither derivable nor made obvious by DeMattos and simply omitted in the argumentation of the Examiner.

In view of the above discussion, it should be readily apparent that DeMattos differs fundamentally from the manner and goal that the present invention conducts to treat AD and the addition of Kojima simply is not combinable with DeMattos and even if one did combine those references, there would not have been a reasonable expectation of success due in large part to the significant and fundamental differences between β2-MG as taught in Kojima compared to the subject matter in the claims.

Reference is again made to Boos et al. disclosing a specific apheresis device but does not compensate for the fact that the combination of DeMattos and Kojima are not combinable and even in combination fail to teach the claimed invention with a reasonable expectation of success as required under the law.

Accordingly, reconsideration and withdrawal of the rejection is requested.

To the provisional rejection citing copending application 11/571,970, in accordance with MPEP § 822.01, Applicants request that:

> If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Allowance of the claims is requested.

Respectfully submitted,

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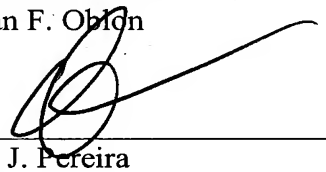

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